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MUMPS ORCHITIS
Byron D. Roseman, M.D. 239

HERPES ZOSTER FACIALIS
J. William Oberman, M.D. and Marshall M. Parks, M.D. .. 254

EDITORIAL: Etiological Considerations of Newly Isolated Viruses
Robert H. Parrott, M.D. 258

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MUMPS ORCHITIS

Byron D. Roseman, M.D.*

The pediatrician may consider himself fortunate in dealing usually with an age group rarely affected by a severe complication of a disease he sees so often. Mumps orchitis is rare before the age of puberty, but at or after this age, orchitis develops in roughly 18 per cent of all men with mumps.[1]

The concern of the pediatrician is, however, not limited to the prepubertal individual. Adolescent medicine is within the pediatric purview, and boys in this age group may readily fall prey to testicular involvement by the virus of mumps.

It is the intent of this communication to review the relatively recent pertinent literature concerning mumps orchitis.

ETIOLOGY

The etiology of mumps *per se* is well known to be a virus which can be directly cultured from patients suffering from mumps.[2] This virus can be made to thrive in monkeys, in embryonated chicken eggs, and in tissue culture. It measures 85–200 millimicrons. It is preservable in the frozen state and in vacuum-dried condition for a period of four years.[3]

Reasons for the apparent sporadic and individual predilection of the mumps virus for the testis have never been truly elucidated although Wesselhoeft,[4] in discussing the matter, notes a connection between vertebrate sex organs and the salivary and facial glands. He describes the crocodile's secretion of a musk-like odor from the facial glands during breeding season, the swiftlet bringing forth mucin from the salivary glands during nesting season (producing a mucin-cemented nest much prized by the Chinese in soup!), and the relationship between sexual activity and enlargement of the facial glands with production of a musky secretion in elephants, camels and antelopes. He thus implicates a remote physiological kinship between salivary glands and gonads. Croisnier[5] speaks of an "elective tropism" of the virus for the testicle, and a "particular orchitogenic propensity." Van den Bon and Herbaut[6] mention viral mutation, season, and fatigue as factors in localization of the virus in the male gonad.

In any case, mumps may be considered to be a generalized disease, virus being present in urine, spinal fluid, saliva,[7] and blood.[2]

Causes of orchitis other than mumps are recorded as: variola, varicella, typhoid fever, influenza, scarlet fever, tonsillitis (*sic*), malaria, pneumonia

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(*sic*), diphtheria, tuberculosis, brucellosis, and septicemia, as well as trauma. Although described,[8] these are all extremely rare.

INCIDENCE

The incidence of orchitis varies from one outbreak of mumps to another. Some observers have opined that the virus is somehow variable, or undergoes mutation such that it may have dissimilar affinity for the testicle in its appearance in different epidemics. The largest most frequently quoted series is a collection from the literature of 8,153 cases of mumps in men, with an incidence of 18 per cent of orchitis.[4] Table I is a sampling of the literature and reflects well the inconstancy of the occurrence of mumps orchitis. Rambar[9] notes that the highest reported incidence is 66 per cent, but the most experienced author in this field, Wesselhoeft,[1] reports that the spread of incidence may be from 1 to 100 per cent.

There seems to be general agreement that the orchitis of mumps is a disease of puberty and beyond. It may, however, occur in infants and children. Stengel,[10] in his search of the literature, found only 5 cases in children less than 12 years old. Werner,[11] in a survey of 2,000 males, found four who gave a history of having had mumps orchitis when 10 years or younger (two cases age 8, two age 10), and Young,[12] in his group of 700 infertile adult males, found three who had had mumps orchitis before age 10. In a similar series, Ballew and Masters[13] report two "well authenticated" cases of prepubertal parotitis with orchitis. Connolly[14] reports the case of a 7 month old boy with mumps orchitis proven by complement fixation test and a demonstrated rise in S and V antibody titers. He mentions one further presumptive case in a 6 month old, and two additional possible cases in male infants less than 1 year old. Riley[15] states that orchitis is a complication in about 1 per cent of children with mumps.

TABLE I

Incidence of Mumps Orchitis in Various Reported Series

Authors	Cases of Mumps	Per Cent Orchitis
Radin[18]	4,397	13.9
Stengel[10]	1,000	18.2
Bailey and Haerem[19]	734	19–21
Candel[43]	244	20.8
Eagles[17]	2,500	25
Candel[23]	142	26
Nixon and Lewis[23]	339	29
Gellis, et al.[44]	502	32
Dermon and LeHew[50]	126	35

Under ordinary circumstances, the patient with mumps involvement of the testis is afflicted unilaterally. Bilateral orchitis is said to occur in 5.4 per cent,[16] 14.8 per cent,[17] 16.7 per cent,[3, 18, 19, 20] 17 per cent,[4] and 33.3 per cent[8] of all cases of orchitis. The frequency seems to vary in different series and years. Hoyne, et al.,[20] suggest a viral predilection for the testicle in some years.

It is interesting to note the experience of one writer[18] who found that when mumps orchitis occurred in cases of unilateral parotitis, the vast majority experienced inflammation of the testicle on the same side. Not all authors record agreement with this observation.[10]

During epidemics, cases of orchitis may occur without apparent preceding or subsequent salivary gland involvement, and in such instances the orchitis is usually of a relatively mild degree.[4] Usually, however, gonadal inflammation follows the height of parotitis by three to seven days, though it may precede by one to nine days, and may occur up to the third week following. Eighty per cent of the cases are said to fall within the first eight days of mumps,[21] and the height of gonadal involvement is usually the third to fourth day.[10] In Eagles' analysis of 2,500 cases seen over a period of four years,[17] the onset of orchitis most frequently occurred about 4.5 days following the onset of parotid swelling, with a range of two weeks prior to 25 days following. Stengel[10] states that this complication has occurred as late as the forty-fourth day.

CLINICAL FINDINGS

Clinical implication of the male gonad by mumps virus is heralded by chills, fever, malaise, headache, and marked weakness. Prostration, delirium, nausea, vomiting and diarrhea may attend. Wesselhoeft's description[4] of the clinical picture bears repetition.

> The patient complains of pain in the testicle, which may range from a slight discomfort and sensation of heaviness to the most intense pain radiating into the thigh, inguinal, or sacroiliac region, and even into the abdomen as a shifting, dull ache. The rapidity of the swelling intensifies the pain which I have heard described as "unbearable." Here the facies become characteristic of a most intense agony, with an anxious, staring expression, accompanied by a hectic look of the cheeks in contrast to the pallor of the rest of the face. The patient groans and appears restless, yet he hardly moves a muscle if he can help it.

Pain is unremitting and nauseating, with characteristic radiation into the thigh and ipsilateral lower abdominal quadrant. The involved organ becomes heavy, tense and exceedingly tender. Epididymis and spermatic cord seem swollen and contribute considerably to pain and tenderness. The scrotum is found to be tense, edematous, and red, with possibly a super-

ficial anesthetic or tingling quality. The cremasteric reflex is invariably abolished.

Simultaneous bilateral inflammation is quite rare, and when present causes marked accentuation of systemic effects. Ordinarily, involvement of one side is followed by an interval, "usually" of two days before contralateral orchitis is apparent.[10] The second testicle may not show evidence of disease until that in the first has subsided.[8]

Very mild cases of orchitis may be manifest as a sensation of increased weight of the testicle, and an occasional patient will complain of local scrotal pain lasting several hours and never develop signs of orchitis. Nixon and Lewis[22] feel that orchitis developing later than 14 days following the onset of parotitis will be rather mild.

Swelling is generally on the wane between the third and sixth day after onset and is no longer evident after another five to seven days.

Prostatitis as an accompaniment of orchitis in mumps may be manifest as a sterile, opaque to yellowish urethral discharge lasting a few days and by prostatic tenderness and swelling on rectal examination.[4] Radin[18] describes this additional complication as uncommon, but occasionally responsible for urinary retention. In a series cited by one author,[1] prostatitis was found in 5 per cent of adult males with mumps. Prostatitis may occur without apparent involvement of the testicle.[13]

A further accompaniment of mumps orchitis, sometimes occurring as an isolated finding, is epididymitis, usually presenting as a swelling the size and shape of a kidney bean. This often occurs before the testicle swells.[18] Candel[16] is of the opinion that this lesion has been neglected and that it is present in 85 per cent of cases of mumps orchitis.

The body temperature, which usually rises to 102°F. and may reach 106°F.,[18] falls by crisis in 50 per cent of those with testicular involvement, and by lysis within 96 hours in the remaining 50 per cent. Stengel[10] however, feels that slow subsidence or lysis, is more common than crisis. Fever lasts 2 to 10 days with an average of three to five.[23] It usually obtains before the patient begins to complain of pain, and with swelling a further temperature rise is apparent. In Eagles' large series,[17] fever lasted an average of three to six days with a range of zero to nine. Petersdorf and Bennett[24] indicate that the fever of this entity is resistant to salicylates, and Hall and Killeen[25] observe that when an attempt is made to eat during the febrile period, vomiting is "not infrequent" in those with severe orchitis. Polyuria as an occasional finding has been described.[18]

PATHOLOGY

Several investigations have clarified the pathologic changes in the testes to be found in this condition. Charny and Meranze,[26] on the basis of testicu-

lar biopsies taken from 2 patients with mumps orchitis on various days from the third to the twenty-first day of the disease, feel that mumps orchitis is an inflammatory process with cellular exudation and destruction of germinal epithelial elements. Leydig cells were not involved. No striking evidence of edema and no evidence of a collection of hydrocele fluid were found. It is emphasized that these findings are not consistent with pressure destruction.

Gall,[27] on the other hand, investigated biopsy specimens from 75 testicles taken at orchidotomies performed by the technique of Wesselhoeft and Vose.[28] The majority of these were obtained within 48 hours of onset, and none later than the fifth day, except that of 1 patient who died on the eleventh day of illness of an unrelated cause. Gall described four distinct phases of inflammation (specimens from 6 patients were histologically normal). The earliest finding (present in 31 cases) was interstitial edema and minimal changes in spermatogenic elements. The second phase, termed "reactive phase," (present in 10 cases) was that of vascular engorgement, perivascular lymphocytic cuffs around capsular arterioles, thickened mural arterioles, interstitial edema, and slightly altered germinal epithelium with some debris in the tubules. This progressed to a third phase (present in 15 cases) with a more dense, more diffuse perivascular cuffing, subcapsular hemorrhage and fibrin deposition, and a focal tubular exudate of polymorphonuclear cells and macrophages. Degeneration of tubular epithelium with ultimate cessation of spermatogenesis and debris filling the tubules were evident. Sertoli cells were generally spared. Intramural exudation of lymphocytes and, later, polymorphonuclear leukocytes was noted. Lesions were felt to be focal, i.e., not involving the tubule throughout its length. In the final phase (present in 13 cases), though still focal, a tendency to diffuseness was apparent. There was dense interstitial lymphocytic exudate, thick fibrin deposition and/or many focal hemorrhages. Viable germinal epithelium was not seen and no Sertoli cells were present. Tubules were thick, and contained a polymorphonuclear leukocytic exudate enmeshed in fibrin. In the material from the one fatal case, pathologic specimens showed the gamut ranging from normal histologic appearance with active spermatogenesis in some areas to progressing fibrosis, hyalinization and organization of tubules.

In the same study there were 18 specimens of material from testicular appendages and epididymides. Inflammation was noted solely in connective tissue elements, and was manifest as perivascular lymphocytic cuffs. No inclusion bodies were seen in any of the material. The author presumes the lesion to "represent a combination of mild inflammatory response to the mumps virus and pressure necrosis inherent upon the architecture of the testis." He suggests from his findings that it would be unusual

for an involved gonad to atrophy completely, but bilateral, fulminant involvement *could* result in complete atrophy and sterility.

COMPLICATIONS

Among the commonly known complications of mumps are presternal edema, encephalitis, pancreatitis, and gonadal inflammation. However, mumps may have many other complications one does not usually consider. Some of these which have been recorded are: conjunctivitis, keratitis, dacryoadenitis, optic neuritis, neuroretinitis, nystagmus, extra-ocular muscular paralysis and disturbances of accommodation, thymic inflammation, thyroiditis, hepatitis, mastitis, bartholinitis, seminal vesiculitis, and arthritis.[4, 9, 24, 29]

Among the complications of mumps orchitis mentioned is orchitis without parotitis occurring during epidemics, often in patients who have had mumps previously.[28] Stengel[10] cites one source to the effect that where mumps orchitis has occurred once, the testes are certain to become involved again in a second episode of mumps.

It has been stated that mumps invasion causes atrophy of no glands other than the prostate and the testicle.[28] Testicular atrophy, manifest as diminution in size and increase in consistency may be evident within four weeks to six months after the acute episode. Ballew and Masters[13] indicate that "atrophy of testicular tissue follows a slow course of months, even years, following subsidence of the acute infection." They further state that as many as 10 years may elapse after the acute phase of the infection before the ultimate result of mumps orchitis may be satisfactorily evaluated. Another writer[8] avers that atrophy is completed in three months.

At necropsy, the mumps-atrophied testicle shows areas of normal tubules with active spermatogenesis, as well as hyalinized or organized tubules.[28] Some degree of testicular atrophy is noted in 40 to 60 per cent of men[10, 16, 28] who have had mumps orchitis. (The figure most frequently quoted is 55 per cent.[16, 28]) Werner[11] has found that the involved gonad may remain distressingly swollen for up to a year. He summarizes the general thesis regarding atrophy, commenting that it may be due to action of the virus on the parenchyma or pressure on the parenchyma by exudate and edema within the taut tunica albuginea.

The question of sterility as a possible sequel to mumps orchitis perennially arises. There are *no* reliable reports of impotence following bilateral mumps orchitis, none of eunuchoidism, none of feminization, and few of sterility, although, at some time and in some form, each has had its supporters. Young,[12] in a group of 700 infertile males, did semen analyses of 124 subjects. Of these, 90 had no history of mumps and 34 a history of mumps but without orchitis. There was no difference in the percentages

with azoospermia or oligospermia between the two groups. Of the entire 700, only 10 had had mumps orchitis, and of these, three had normal sperm counts. He concludes that "mumps orchitis cannot be regarded as a serious cause of male infertility in view of the small number of men affected by it." Ballew and Masters,[12] in a study of 79 infertile couples found 19 men with histories of mumps orchitis, 15 of whom were studied minutely. Nine of these were azoospermic and six demonstrated oligospermia together with an increased number of abnormal forms. In all 19 there was some degree of testicular alteration. The authors noted that unilateral involvement is supposedly not etiologic of sterility but some of their cases showed sperm counts "so low that sterility was almost inevitable." Werner,[11] in contrast, felt that on the basis of his similar study, "mumps orchitis cannot be regarded as an important cause of sterility in the male population."

Wesselhoeft[4] implies that mumps prostatitis and subsequent atrophy may be a more frequent cause of sterility than orchitis. This has been discussed in a similar vein by others.[11, 13]

Gilbert[30] reviewed 5,500 cases of testicular tumors. In 24, or 0.43 per cent, of these he found histories of mumps orchitis and subsequent atrophy, and in 80, or 1.45 per cent, tumors associated with nonspecific atrophy (following trauma, ectopy, developmental anomalies). The mean interval between mumps orchitis and diagnosis of tumor was 12 years. In the group with histories of mumps, 13 of the tumors were unicellular in type, nine teratoid, and two miscellaneous. He concluded that there was no relationship between mumps orchitis and testicular neoplasm.

Several authors,[4, 10, 11, 31] describe occasional cases of persistent, post-inflammatory, neuralgic pain in affected testes; this is usually vague in nature but is occasionally intense. There is no known explanation for this phenomenon.

DIAGNOSIS

The clinical diagnosis of orchitis due to mumps should be no great problem, particularly in the presence of evident parotitis, orchitis occurring during epidemics of mumps, and/or a history of exposure to mumps. Without parotitis, the appearance of orchitis two to three weeks following exposure is "highly suggestive" of mumps etiology.[23] Other diagnostic criteria for isolated mumps orchitis are cerebrospinal fluid pleocytosis and elevated serum amylase or urinary diastase.[13] Wesselhoeft and Vose[28] feel that with isolated involvement, diagnosis is a function of a history of exposure, an incubation period of approximately 18 days, and the clinical course.

Differential diagnosis of isolated mumps orchitis from torsion of the testicle has been emphasized.[14, 28] In testicular torsion, a relatively rapid

onset of symptoms with nausea, vomiting and possibly shock, will serve to differentiate.

In the laboratory, diagnosis of mumps (or isolated mumps orchitis) may be confirmed by demonstrating a rise in S and V antibody titers in the course of the disease, or by isolation of the virus from material taken from the patient. Utz, et al.,[7] have recently described tissue culture techniques as a facile method for isolation of the mumps virus in a properly equipped laboratory. Presumptive diagnosis on the basis of cytopathogenic changes may be made as early as three days after culture inoculation. These workers isolated the virus from urine and saliva as early as the second day of illness and from the urine as late as the thirteenth.

TREATMENT AND PROPHYLAXIS

The most controversial facet of mumps orchitis is therapy. As with therapeutic regimes for many disease processes, "many are called, but few are chosen." Treatment and prophylaxis methods currently popular or thought to be of value include surgery, feminizing hormones, adrenal cortical steroids, and gamma globulin.

Surgery was apparently first advocated in 1864 by Smith[32] who advised multiple punctures of the tunica albuginea for gonorrheal orchitis, stating that such surgery had been in vogue in Paris for two years. Schottmüller,[28] in 1904, is said to have suggested incision of the tunica vaginalis and tunica albuginea for mumps orchitis.

Wesselhoeft and Vose[28] in 1942, described incision of the tunica albuginea early in the course of mumps orchitis resulting in immediate relief of symptoms. Their 13 patients did well with little evidence of atrophy. Ballew and Masters[13] found that incision of the tunica vaginalis with Penrose drainage of hydrocele fluid was successful in 68 patients with mumps orchitis. These investigators believed that adhesions formed between the tunicas albuginea and vaginalis, limiting expansion of the edematous parenchyma. This was verified at surgery in a number of their cases. The authors felt that early surgery as described was "sufficient to insure optimum results" and prevent atrophy. Pinck[33] reported 8 cases treated surgically, half by multiple incisions of the tunica albuginea and half by incision and drainage only of the tunica vaginalis. Adhesions were not found to be important. Results were satisfactory in both groups. The author suggested that atrophy, when it occurs, it is not due alone to primary orchitis, but "rather is the result of a rapidly forming, strangulating hydrocele." Burhans[31] states essentially the same thesis. Campbell[8] advocates prompt, early incision of the tunica vaginalis and extensive incision of the albuginea layer. Surgery is advocated by others for acute, bilateral testicular involvement.[6]

Surracco and Lockhart[34] seem impressed with the need for incising the enveloping layer of the spermatic cord on the basis of their finding a return of normal color and vascularity of the cord with this procedure. On the other hand, Candel[16] declares that surgery is of no proven or demonstrated value.

The thread which runs consistently through the surgical cloth is a plea for early intervention. In all cases so supported, little testicular atrophy appears in those patients followed postoperatively. In this regard, the biopsy findings of Charny and Meranze[26] lead them to believe that surgical intervention on or after the third day will not prevent tubular destruction.

Solem[35] in 1954, treated 6 cases of mumps orchitis with ACTH and found prompt subsidence of inflammation in 5. The rationale for use of this medication was "blockage of the exudative tissue reaction with a reduction of cellular inflammatory reaction." In another series,[36] 14 patients were treated with cortisone, beginning with a dosage of 300 mg. the first day and gradually decreasing it to 150 mg. per day for maintenance. It was found that inflammation diminished and there was good symptomatic response, but there was no evidence that the "natural course of orchitis is shortened by the use of cortisone acetate." Risman,[37] reporting 5 cases treated with similar dosage of cortisone, found that the agent did not affect duration of swelling, or the febrile response, or prevent development of contralateral orchitis during therapy in 3 of the 5 cases, though pain and tenderness were ameliorated within 24 hours in all.

Petersdorf and Bennett[24] report a uniformly satisfactory clinical response in 23 cases treated with 300 mg. of cortisone the first day and 200 mg. subsequent daily maintenance. These authors regard steroids as the treatment of choice in spite of the absence of control cases. They mention the earlier work done and attribute poor results to inadequate dosage.

Another study by Zeluff and Fatheree[38] done on 4 cases with either hydrocortisone, ACTH or prednisone prompted the authors to advise early institution of steroid therapy in all cases of mumps orchitis. An outcome of lessened severity of the lesion with less marked atrophy is implied. The authors speculate that exhibition of steroids at the inception of parotitis may prevent gonadal mumps.

Kinsell and Jahn[39] feel that steroid therapy in this entity brings about rapid dissolution of inflammation and may, if instituted early enough, prevent residual damage. Spink[40] records advocacy of cortisone or hydrocortisone in severe cases only and feels that marked improvement in pain, swelling and temperature is evident in 24 hours. He emphasizes the need to maintain treatment for as much as a week to prevent recrudescence.

A recent paper by Smith and Bishir[29] analyzes the results of steroid therapy in 51 patients, 20 receiving ACTH in doses varying from 25

mg. intravenously in a single dose, to as much as 500 mg. in divided intramuscular doses, and 31 receiving cortisone orally in dosages from 50 to 100 mg. four times daily. There were 34 controls. ACTH had no salutary effect relative to the controls. Cortisone did not prevent involvement of the opposite testicle during treatment, and 9.8 per cent of the hormone-treated group developed complicating bacterial infections, while the controls had none. The conclusions reached are of great interest: the dose of ACTH was considered to have been less than adequate, and the importance of optimum cortisone dosage was stressed. In the cortisone-treated group the duration of pain was significantly less statistically than in the controls, though the duration of swelling, fever and hospitalization were not statistically different. It was "debated whether the analgesia obtained was worth the infections incurred." Recent editorial comment[41] casts further doubt on the validity of empirical steroid therapy in general and emphasizes some of its inherent hazards.

Estrogens, usually in the form of diethylstilbestrol, have been used with variable results. Van den Bon and Herbaut[6] insist that they be used preventively in all males who have passed puberty when mumps is diagnosed. Croisnier[5] suggests that the synthetic estrogens are indispensable in all cases of mumps in young adult males. The rationale for their use is considered by most authors to be an induced reversion of the testis to the prepubertal state, or "repose".[37] Considering the low incidence of prepubertal mumps orchitis, estrogen prophylaxis would be invaluable were the hypothesis clearly demonstrable. Such a demonstration however, has not been made.

Savran[42] studied 245 male patients with mumps and gave to each 1 mg. of diethylstilbestrol by mouth daily for five days. Of these, 18.2 per cent developed orchitis. Of the 168 controls, 25.5 per cent developed mumps orchitis. Another study by Hall and Killeen,[25] similarly conducted with the same drug, utilized 63 treated cases and 34 controls with a finding of no significant difference in the incidence of orchitis in the two groups. It was suggested however, that there may be some clinical value in using the drug prophylactically. Norton[21] using this agent both therapeutically and prophylactically found no significant difference in treated and control groups. It was felt that diethylstilbestrol has no prophylactic value but may decrease the duration of fever and degree of swelling and discomfort. The outcome in a series using both treated cases and controls led Hoyne, Diamond and Christian[20] to believe that their results of treatment with diethylstilbestrol were "dramatic and consistent" using 2 mg. daily for prophylaxis and 5 mg. per day for treatment.

Candel[43] noted that blood and plasma had been used by various investigators for treatment and prophylaxis since 1915 with equivocal results. He

reported a study using 244 male patients with mumps, the treatment group receiving 50 ml. of pooled normal gamma globulin by intramuscular injection. Forty-seven per cent of controls developed orchitis while only 25 per cent of the treated group contracted it—a statistically significant difference. It was noted also that a dose of 25 ml. of gamma globulin was of no value! Gellis, et al.,[44] studied an outbreak of mumps among soldiers. Gamma globulin said to have an antibody content 25 times that of plasma was made from convalescent patients within three months of recovery from the disease. Twenty milliliters of this material was given by the intramuscular route to alternate patients with parotid swelling present less than 24 hours. Of 51 men so treated, only 7.8 per cent developed orchitis contrasted with 27.4 per cent of 51 controls. A duplicate of this study done with gamma globulin made from pooled normal plasma showed the latter material to be of little value.

Sundry investigations into the use of pooled plasma and serum as prophylactic agents against orchitis in mumps have been reported,[9, 19, 23, 45] all with varying findings. Bailey and Haerem[19] collected serum from donors three weeks following the onset of mumps. They gave either 10 or 20 ml. of unpooled material by intramuscular injection to patients with mumps within the first three days of parotid swelling. Of the controls, 19.9 per cent (110 patients) developed orchitis and 15.3 per cent of the experimental group (183 cases) were so affected. This work has been confirmed subsequently.[18] An incidental finding in the former study was a lower incidence of mumps orchitis in patients receiving serum made from donors who had had orchitis, 4.2 per cent, or 2 out of 48, as against 19.2 per cent, or 26 out of 135, in those receiving serum from donors who had parotitis only. There was no salutary effect demonstrable using such biologicals therapeutically.

The recent literature contains other therapeutic recommendations. Antibiotics have been used[46] but have proven to be as disappointing as in other viral infections.

Leineberg,[47] during an epidemic of mumps in troops, found potassium bromide in a dosage of 3 Gm. daily *before the onset of mumps* to be of value in decreasing the incidence of orchitis in patients who contracted mumps. Only 18.2 per cent of 110 men so fortified developed mumps orchitis, while 32.6 per cent of 110 not given potassium bromide experienced the complication.

General symptomatic measures to be considered are bed rest, testicular support, cold applications, and analgesia. Most authors[18, 20, 21, 23, 35] agree, incidentally, that bed rest during clinical parotitis is of no value in preventing the development of orchitis. It is certain, however, that a patient with orchitis will wish to, and should, remain at rest, and may even require narcotics for alleviation of severe pain.

Further comment is deserving in regard to more specific prophylactic measures. Obviously it would be desirable to avoid mumps entirely, but at the present state of knowledge this is neither practical nor possible. Mumps vaccine is prepared by growing the virus in embryonated chicken eggs and then inactivating the virus with ultraviolet light or formaldehyde. The duration of immunity endowed by the antigen is uncertain but is probably not longer than one year. It is unknown whether or not vaccine given within two to three days of exposure can abort or modify mumps, but antibodies are detectable in the blood within one week following injection. Its use is not justified in children, in whom the disease is usually mild, though it is advisable to immunize male adults who have a negative mumps skin test (and/or an antibody titer so low as to indicate susceptibility) during epidemics or under crowded conditions. The dosage recommended is two subcutaneous injections of 1 ml. given at one to four week intervals. Booster doses should be given every six months for maintenance of antibody levels.[48]

Next in order of desirability would be induction of this "childhood disease" or immunity thereto in childhood. As far as mumps is concerned this has not been approached in practical fashion. Stokes,[49] however, suggests a measure which has implications for further study. He suggests inoculation of newborn infants by the oral or respiratory route with virus of various disease entities when there is assurance of the presence of maternal antibodies.

Twenty to 40 per cent of mumps is subclinical[3] and it would be manifestly important in certain situations to discover such cases. The skin test, material for which is prepared identically with the vaccine, is useful here. This intradermal test yields a tuberculin-like reaction: an area of induration and redness greater than 10 mm. in diameter occurring in 24 to 36 hours is indicative of immunity.[3] The skin test dose is 0.1 ml. given by intradermal injection; no control substance is injected. Mumps vaccine and repeated skin tests apparently do not affect the skin test reaction, though in the diagnosis of a problematic case of mumps the test is of no immediate value; skin test sensitivity does not develop for weeks or months following the disease. As with the vaccine, this material should not be used in individuals known to be sensitive to chicken, eggs, or chicken feathers.[50]

SUMMARY AND CONCLUSIONS

Mumps orchitis is rare before puberty. About 18 per cent of men with mumps will develop orchitis. It is not known why the mumps virus attacks the testicle only sporadically though the disease is generalized, with virus demonstrable in blood, spinal fluid, urine and saliva.

The incidence of orchitis varies in different epidemics and years; it has

been postulated that viral mutation may be responsible. Bilateral gonadal involvement is also inconstant but is said by the larger number of observers to occur in about one-sixth of the cases of orchitis.

Orchitis usually befalls the patient within the first week or so of mumps and is most severe in the third or fourth day of testicular swelling. Characteristic are marked local testicular swelling, tenderness, and pain which radiates variously in a patient who shows the signs of a severe systemic illness. Temperature, which may be as high as 106°F., falls by crisis in about half the cases and usually lasts three to five days. Prostatitis accompanies mumps orchitis in 5 per cent of cases and epididymitis in 85 per cent.

Mumps orchitis is found to be a focal inflammatory lesion which may lead to organization of tubules and obliteration of germinal elements. The ultimate effect may be a combination of parenchymal inflammation due to direct action of the virus, and pressure necrosis.

Some degree of testicular atrophy follows orchitis in 40 to 60 per cent of cases and may be evaluated properly only after an interval of months.

Sterility resulting from the orchitis of mumps is undoubtedly a most unusual complication, to be expected only following the most severe, fulminant, bilateral inflammation. There is no apparent relationship between mumps orchitis and testicular tumors.

The clinical diagnosis of mumps orchitis should be made with facility. Isolated mumps orchitis is diagnosed on the basis of a history of exposure, a two to three week incubation period, clinical course, spinal fluid pleocytosis, an elevated serum amylase, a rising antibody titer, and characteristic cytopathogenic changes in tissue culture of isolates from urine, spinal fluid, or saliva.

There is little agreement regarding therapy. Of all forms, experience with orchidotomy has been the most extensive, and when done before the third day of orchitis, has had apparent success in relieving symptoms promptly and in preventing atrophy. Generally, early incision and drainage of the tunica vaginalis in severely affected patients would seem to lend most satisfactory results. Intervention after the third day is not of value.

Steroid therapy has many champions. When used, dosage should be adequate and maintained for a sufficiently long period to prevent exacerbation. The exhibition of corticoids in mumps orchitis has *not* been shown to prevent contralateral inflammation of an uninvolved testicle. The usual hazards of steroids are possible and one recent investigation stresses the increased incidence of various bacterial infections in a steroid-treated group.

Advocates of estrogens, usually in the form of diethylstilbestrol, feel their use causes a reversion of the testicle to the prepubertal state, thus suggesting a prophylactic as well as a therapeutic value. It is difficult to

be conclusive about their use, though some investigators are convinced of their worth. Further controlled study is certainly warranted.

Where mumps immune gamma globulin is available, or facilities are at hand for its processing from immune or convalescent plasma, its administration to men at the inception of mumps is of definite prophylactic value.

Mumps vaccine *may* prevent or modify mumps if given within two to three days of exposure. To maintain immunity it must be given at six month intervals. The skin test antigen, giving a tuberculin-like reaction, will prove helpful in identifying the 20 to 40 per cent of mumps which is subclinical and those subjects in need of immunization.

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HERPES ZOSTER FACIALIS

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Herpes zoster is a specific acute infectious disease caused by a virus which is identical in size and shape to that of the varicella virus. Herpes zoster is frequently noted to be a source of varicella in children and varicella may induce herpes zoster in exposed adults. Both diseases may occur at the same time in the same child, and adults may contract herpes zoster, having previously had varicella as a child.

Clinically, herpes zoster presents as a selective inflammation of the posterior root ganglia accompanied by an erythematous vesicular eruption within the corresponding dermatomes. Variants include: 1) a poliomyelitis-like involvement differentiated by its unilaterality and segmental distribution and by greater posterior root involvement, 2) a relatively mild leptomeningitis, and 3) a true peripheral mononeuritis with both sensory and motor manifestations.

The disease is not uncommon in children and is reported to cause somewhat less than one per cent of all skin disease occurring in childhood. The occurrence is usually sporadic although a number of epidemics have been reported. The incubation period ranges from one to three weeks.

The first symptom of the disease is usually a cutaneous hyperesthesia, ranging from mild to severe in degree and corresponding to the affected dermatome. This may be accompanied by a slight fever and mild constitutional symptoms. Three to four days later, a number of erythematous itching patches are noted over the hyperesthetic areas; these rapidly develop into small vesicles filled with clear fluid resting on an erythematous base. The vesicles become turbid and then dry up and crust over. There

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may be an accompanying inflammation of the regional lymph nodes. The acute phase of the disease usually lasts a week or less.

Lesions are practically always unilateral and may affect one to three dermatomes. Sites of predilection include the thorax, abdomen, neck, shoulders, thighs, buttocks, and face. Rarely are lesions found distal to the elbows or knees.

Occasionally, the following features may obtain: 1) During the acute stage, a stiff neck or other signs of meningeal irritation may be present. The spinal fluid may contain over 100 cells, most of which are lymphocytes. 2) Secondary infection with ulceration and severe scarring may result. 3) A severe postherpetic neuralgia may persist. This is rare in children. 4) Localized paralysis and muscle atrophy may develop. This may occasionally be permanent. 5) Symptoms of irritation of the parietal peritoneum or pleura, or of the urinary bladder may occur. 6) Herpes zoster may be secondary to insult to the dorsal nerve root by the lesions of such conditions as arsenic poisoning, tuberculosis, tumors, and leukemia.

The cranial nerves are not infrequently affected. Paralysis is more common when this occurs and has been estimated to exist in about 50 per cent of cases affecting cranial nerves. In a few cases, optic neuritis or paralysis of the third, fourth or sixth cranial nerve has been described. When the geniculate ganglion of the seventh nerve is involved, permanent facial paralysis may result. This may be associated with loss of taste and herpetic lesions over the concha of the ear and in the external auditory canal. Less frequently, the eruption occurs over the anterior two-thirds of the tongue, hard palate, and anterior pillars.

The fifth cranial nerve is by far the most commonly affected, involvement of the gasserian ganglion accounting for 19 per cent of all cases of herpes zoster observed in one large series. In the great majority of cases in which the trigeminal nerve is affected, the ophthalmic division is involved. Vesicular lesions under these circumstances may occur on the upper eyelid, conjunctiva, and cornea. Involvement of the cornea is the most serious complication of this form of herpes zoster since the resultant keratitis may cause permanent scarring of the cornea.

CASE REPORT

N. P., a 6 year old white girl who is a physician's daughter, was admitted to Children's Hospital on June 15, 1957, with a three day history of a painful rash on her right cheek and around her right ear.

Her previous general health had been good. At age 5 months she had a few mild vesicular lesions on her body at the same time that clinical varicella appeared in two older siblings. Other childhood diseases included rubeola and mumps from which she recovered without incident.

Three days prior to admission to the hospital she felt pain over her right ear;

this was accompanied by the appearance of erythematous papules on her right cheek and right ear. Over the succeeding three days these papules gradually changed to vesicles which then tended to become confluent. She complained of earache and tooth pain which became increasingly more severe.

On admission to the hospital she appeared to be a well developed, well nourished child who was in considerable pain. Her rectal temperature was 102.2°F. There were large bullous lesions covering her right ear, cheek, and chin (fig. 1). These lesions were surrounded by areas of edema and erythema. A few additional small grouped vesicles were noted on the right side of the buccal mucosa, tongue, anterior pillar of the right tonsil, and the posterior aspect of the right tympanic membrane. The skin of the right upper eyelid was also involved, but the conjunctiva and cornea were not. There were enlarged tender right posterior cervical glands. The left side of the face was not involved in the pathologic process. The remainder of the physical examination was normal.

Initial treatment consisted of gavage feedings and sedatives together with the oral and local administration of broad spectrum antibiotics, and the intramuscular injection of gamma globulin. She became afebrile 48 hours following admission. During the five days of hospitalization the lesions gradually crusted over and the pain diminished.

Subsequent to her discharge from the hospital, her lesions gradually healed although two lesions in the scalp and one in the ear were still present four months after discharge. These were, however, probably the result of irritation from scratching. For six to eight weeks after hospitalization there was intense itching over the involved area, severe enough to require sedation at bedtime. Seven months after onset, slight bluish pigmentation over the involved areas remained; these areas continued to be overly sensitive to touch.

FIG. 1. Herpes zoster at the height of the eruption

COMMENT

Dr. Parks:

Apparently the mandibular division of the trigeminal nerve plus the zygomatic branch of the maxillary division were affected in this patient. The ophthalmologist is primarily concerned in gasserian ganglion inflammation when there is involvement of the infraorbital branch of the maxillary division which supplies the inferior conjunctiva and skin of the lower lid, and any part of the ophthalmic division. Herpes zoster frequently affects only the ophthalmic division and in such cases the name herpes zoster ophthalmicus is used.

Herpes zoster ophthalmicus can affect one or all three branches of the ophthalmic division: the lacrimal which supplies the skin and conjunctiva of the temporal side of the upper lid and the lacrimal gland; the frontal which supplies the skin and conjunctiva of the middle and nasal regions of the upper lid and the skin of the forehead; and the nasociliary which supplies the medial canthus, conjunctiva and surrounding skin, anterior part of the nasal mucosa and the skin over the tip of the nose, plus the cornea and uvea of the eye. The grave ophthalmological problems are generally contingent upon nasociliary branch involvement. Therefore, pain in and on the tip of the nose and in the eye followed by the occurrence of bullae on the nose, keratitis and iridocyclitis carries a very poor prognosis since the usual late sequelae, corneal scarring and atrophy of the iris and ciliary body, preclude good vision. In fact, often the end result is a blind, painful, degenerated eye that requires enucleation.

Since all treatment is of little value, the ophthalmologist can do little to alter the visually destructive course of this disease. Herpes zoster of the gasserian ganglion is a dreadful disease; however, there is reason to rejoice when the nasociliary branch of the ophthalmic division is not involved.

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EDITORIAL

Etiological Considerations of Newly Isolated Viruses

Robert H. Parrott, M.D.*

With the application of tissue culture methods and refined serological methods to the virus field, many more new viruses are being associated with the respiratory system than there are well defined clinical and epidemiological entities with which to match them. However, certain principles for linking viruses with disease have evolved, primarily from a team approach wherein the thinking of virologists, epidemiologists and clinicians is combined.[1] In attempting to link a new or unknown virus with respiratory tract illness one must first be sure of the nature and characteristics of the virus Next, he must be sure of the presence of disease and preferably the distinctness of clinical features. Thirdly, he must be able to show that the particular virus is associated with the particular clinical picture more often than would be expected by chance, and be able to reproduce the disease in man by virus inoculation or show that the disease is associated with the virus regularly at different times and in different locales. If the pediatrician will keep the above principles in mind as he encounters the frequent reports of possible association of new or old viruses with illness, he will be able to examine these reports more objectively and to remain reasonably abreast of this rapidly changing field without becoming confused.

In recent years at least nine viruses or groups of viruses other than influenza have been reported as possible causes of respiratory tract disease. These include the large group of adenoviruses, the group A Coxsackie viruses, certain miscellaneous viruses such as the respiratory syncytial virus, "2060" virus, "J.H." virus and an ECHO virus, "JV-1," as well as the following myxoviruses: the croup-associated virus, the hemadsorption viruses and Sendai viruses (newborn pneumonitis virus, hemagglutinating virus of Japan or Influenza D). All of these agents have been recovered from the respiratory tract of children or adults in association with respiratory tract symptoms. However, more is known about some than about others in their etiological relationship to respiratory tract illness.

The adenoviruses, for example, are prevalent agents found in the respiratory tract; the group includes the cytopathogenic agents which were originally isolated from tonsils and adenoids and other related viruses which have subsequently been found in cases of conjunctivitis and pharyngitis, and from fecal material and certain tissues at necropsy.[1] There is good evidence that one of the adenoviruses, type 3, causes pharyngoconjunctival

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fever, an acute illness characterized by fever, pharyngitis, conjunctivitis and posterior cervical lymphadenopathy. This illness may be considered clinically distinct when most of the features are present or when an epidemic is occurring. In addition, adenoviruses types 4 and 7 cause acute febrile disease of the respiratory tract in military recruits. This is characterized by fever, chills, headache, generalized aches and pains, hoarseness and irritated throat. Symptoms are considered relatively specific by those dealing with military personnel. This association of types 4 and 7 viruses with illness has not been borne out frequently in children and in fact, types 4 and 7 viruses rarely have been isolated from children. Apparently adenoviruses types 1, 2, 3, 4, 5 and 7 may also cause nonbacterial pharyngitis, but sufficient cases have not been reported to allow a full clinical description. These viruses, particularly types 1, 2 and 5, have been found in up to 90 per cent of tonsils and adenoid specimens from several parts of the world. This leads to the speculation that after an acute infection with adenoviruses, a patient may harbor the virus in a "latent" state for an indefinite period of time.

The clinical relationship of certain group A Coxsackie viruses to a particular type of vesicular pharyngitis in children, herpangina, is now well accepted.[1] The virus types have been consistently the same—A-2, A-4, A-5, A-6, A-8, and A-10.

Two newly isolated myxoviruses, hemadsorption virus types 1 and 2, have recently been reported, and controlled studies strongly suggest an etiological association with respiratory tract disease in children. Between October 1957 and March 1958 in the Washington, D.C. area, approximately 15 per cent of infants less than 1 year of age seen in an out-patient department because of acute affections of the respiratory tract and 0.5 per cent of controls were infected with one of the hemadsorption viruses. In addition, up to 33 per cent of infants with a "croup syndrome" were infected with type 2 hemadsorption virus.[2, 3] If this frequency of association is borne out in future studies, then hemadsorption viruses may be among the most prevalent causes of respiratory illness in children.

Reported studies on the other viruses mentioned have not been large enough, nor are there sufficient controlled epidemiological data from different times and places yet to be at all definitive about the frequency with which these viruses cause respiratory tract disease. The croup-associated agents have been isolated in several parts of the world from children with croup as well as from children with other manifestations of respiratory tract illness.[4] In one survey, 90 per cent of adults had hemagglutination inhibition antibodies against these viruses. Sendai virus has been found in association with pneumonitis in infants, a meningitis-like syndrome in infants, and an influenza-like illness in adults.[5] Some antigenic stimulus for

this virus is relatively prevalent in the United States, 40 per cent of all serums tested in one study showing significant hemagglutination inhibition titers.[6] Since this agent is serologically related to hemadsorption virus type 2 by complement fixing but not by hemagglutination inhibition and neutralization antibody tests, it is possible that the hemadsorption agent is that stimulus. The respiratory syncytial virus, identical with a causative agent of coryza in chimpanzees, was recovered from an infant with bronchopneumonia and a suggestive association shown between this virus and bronchopneumonia occurring in children visiting an out-patient department in Baltimore.[7] The serums of 80 per cent of children 4 years of age possessed neutralizing activity against the recovered agent. An association between ECHO virus JV 1 and mild respiratory illness has been reported in six children, 5 to 14 months of age, in an apparent outbreak of infection with this agent in a nursery group.[8] In two different outbreaks the "2060" virus was recovered from naval recruits with mild respiratory illness, and a total of 16 out of 47 affected patients showed a rise in neutralizing antibody to this virus in their serums following the illness. The prevalence of antibody to "2060" virus increases with advancing years.[9] JH virus has been described in association with symptoms of low grade fever, malaise, coryza, sore throat and a cough.[10] Twenty per cent of serums from individuals over the age of 8 showed neutralizing antibody to this virus. There is some evidence to suggest that the "2060" virus and JH virus are serologically related to each other.

Most of those working with newly isolated respiratory viruses share the opinion that any of several newly isolated viruses may affect the upper respiratory tract in a common way, and that similar illnesses may at different times be caused by different viruses. There is no doubt, however, that a great deal of combined clinical, laboratory and epidemiological study is necessary before a final picture can be drawn.

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